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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,988	02/03/2006	Gary Michael Ksander	PC/4-33209A	6747

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EXAMINER	
COPPINS, JANET L	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,988	KSANDER ET AL.	
	Examiner	Art Unit	
	JANET L. COPPINS	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-11,13 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3-7,9-11,13,21 and 26* is/are allowed.

6)☒ Claim(s) *22-25 and 27* is/are rejected.

7)☒ Claim(s) *1 and 2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7, 9-11, 13, 21-27 are pending in the instant Application.

Information Disclosure Statement

2. Applicants' Supplemental Information Disclosure Statement, in which copies were supplied of all non-patent literature and foreign documents, has been considered by the Examiner. Please refer to the signed copy of Applicant's PTO-1449 form, submitted herewith.

Response to Amendment

3. Applicant's Amendment and Response, submitted October 8, 2008, has been reviewed by the Examiner and entered of record in the file. Accordingly, claims 8, 12, and 14-20 are cancelled, and claims 1-4, 7, 9, 13, 21 and 27 have been amended.

Previous Claim Rejections –

35 USC § 103

4. Claims 1-13 and 22-27 previously rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,045,540, issued 09/03/1991. In view of Applicants' amendments to the claims, in order to specifically limit "W" to oxazole, the obviousness rejections have been overcome and are withdrawn.

35 USC § 112

5. Claim 27 previously rejected under 35 USC 112, second paragraph, for reciting the limitation "The pharmaceutical composition according to Claim 25. . ." since Claim 25 is drawn to a method, not a composition. Applicants have amended claim 27 to depend from claim 26, therefore the indefiniteness rejection is withdrawn. However, please refer to the following enablement rejections, which encompass claim 27.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 22-25 are rejected under 35 U.S.C. 112, first paragraph, because the Specification does not reasonably provide enablement for using compounds of formula (I) for the treatments listed in these claims. Therefore, the Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

Regarding claim 22, Applicants have not provided evidence that supports their arguments that one skilled in the art would be know how to perform the claimed method for treating a specific disease or diseases of **real world relevance.** Claim 22 is directed to a method, "of activating PPARs in any mammal" and claim 23 is drawn to a method for treating "conditions mediated by PPARs," yet the claims fail to meet the requirements for "how to use" under 35 U.S.C. 112, first paragraph, as stated above. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility, or a well established utility (i.e. the

claim does not recite a specific disease or types of diseases that may be treated), one skilled in the art clearly would not know how to use the claimed invention. Claims 23 and 24 are drawn to methods of treating any or all conditions which are mediated by PPARs in a mammal. Claim 25 is drawn to a method of treating a wide variety of diseases, encompassing *any* or *all* vascular diseases, respiratory diseases, as well as cancer and Alzheimer's, for example.

The level of skill in the art

Those practitioners who treat disorders of this type (medical clinicians, pharmacists and/or pharmaceutical chemists) presumably would be highly skilled in the art.

The state of the prior art and the predictability or lack thereof in the art

There is no question Applicant's pyrrolidine-dicarboxylic acid compounds may play a role in future methods of treating the aforementioned diseases/disorders affected by PPARs. What is disputed is the claim that the compounds of formula (I) could be taken by a person of ordinary skill in the art at the time of filing and be used as treatments for the diseases/disorders recited in claims 22-25, without undue experimentation. At the time of filing or even at present, the most which can be said about the compounds of formula (I) is that certain of the compounds possess the ability to bind PPAR *in vitro*. Moving from a discovered mechanism of action to a method of treatment requires a fallacious, inductive leap of logic amounting to undue experimentation. There is simply no evidence to be found in the literature suggesting that Applicant's compounds, or their structural cousins, are capable of being used in the manner claimed in Claims 22-25. In essence, there is no absolute predictability in pharmacology, even with compounds whose properties have been determined, despite the extraordinarily high skill possessed by the ordinary artisan.

Further, with respect to the treatment of cancer, which is encompassed by claim 25, Dermer (Bio/Technology, 1994, 12:320) teaches that, "□etri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Further, it is also the state of the art that there is no known cure or prevention for Alzheimer's disease, furthermore, there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, ARICEPT®, EXELON®, REMINYL® and COGNEX®, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. MEMANTINE®, which blocks excess amounts of glutamate, treats late stage Alzheimer's disease.

(<URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>).

The amount of direction or guidance present, and

the presence or absence of working examples,

Applicant provides no working examples which support the claim to a treatment of any specific condition or disease. Rather, Applicants provide *in vitro* PPAR binding data. Those of skill in the art recognize that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking.

The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, lnc., 1983, New York, p4) teach that it is recognized in the art that many differences exist between cultured cells and their counterparts *in vivo*.

These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from

which the cells were derived. This result has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro).

The breadth of the claims

Applicants are claiming methods of treating an extremely broad number of diseases or conditions, please refer to the "laundry list" recited in claim 25. Applicants have provided evidence that the compounds are effective for activating PPAR binding within certain cell lines, however "the selection of the examples…used as the disclosure to support a claim must be adequately representative of the area covered by it," please see *In re Cavallito et al.* (CCPA 1970) 429 F2d 452, 166 USPQ 552. Therefore the instant specification is lacking significant data to accommodate as many diseases or conditions as the claims are alleging by broadly reciting, "A method for the activation of Peroxisome Proliferator-Activated Receptors, comprising…."

The quantity of experimentation needed

Another deficiency necessary for a person of ordinary skill in the art to use Applicant's compounds to treat the recited diseases/disorders is dosage. So far, there is very little, if any, information to be gleaned from the literature on the subject of dosage relating the instant claimed pyrrolidine derivatives to *each* and *every* of those diseases/disorders sought to be treated in the instant Application. There does not seem to be enough knowledge in the art to connect the compounds' properties to the actual treatment of the diseases/disorders claimed. It does seem that certain pyrrolidine compounds capable of binding PPARs may provide useful therapeutic tools in future. Although, at the time of filing, and even at present, a person of ordinary skill in the art would not be able to use the invention as claimed.

8. Claims 24 and 27 rejected under 35 U.S.C. 112, first paragraph, as not being fully enabled. While various active ingredients may be listed in the specification, the claims are not enabled for any additional therapeutically effective amount of an agent, as recited in the laundry lists of claims 24 and 27, since there is no indication as to the full range of additional therapeutic agents that could be utilized.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described above.

The nature of the invention

The nature of the invention is a combination product, containing a compound of claim 1 and an additional therapeutic agent, selected from the lists recited in claims 24 and 27. Claim 24 is drafted in terms of a method of use and claim 27 is directed to a pharmaceutical composition.

The state of the prior art and the predictability or lack thereof in the art

It is well recognized in the medical art that treatment of diseases or symptoms are not analogous terms. The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. Also, in the absence of a showing of correlation between all of the potential therapeutic agents encompassed by

claims 24 and 27 and the compound of claim 1, one of skill in the art is unable to fully predict possible results from the administration of the claimed compounds.

The amount of direction or guidance present and the presence or absence of working examples

Treatment of specific diseases or disorders is normally disease or symptom oriented, thus are highly individualized, i.e. a composition for treating inflammatory joint pain would not employ the same agents (requires an additional NSAID agent) as a composition for treating inflammatory bowel disease (requires an additional 5-ASA). If Applicants allege that treating said disorders benefit from binding PPAR, then Applicants must demonstrate that a composition for activating the biochemical pathway of PPAR and all of the possible combinations of compositions of claims 24 and 27 are inexorably linked. Applicants have provided no support whatsoever in the Specification for the additional "therapeutic agents" recited, other than the "laundry list" described on pages 35-36 of the Specification. The efficacy of a pharmaceutical composition intended for treatment of a specific disease/disorder needs to be specifically and individually supported by factual evidence. The data provided in the disclosure is insufficient evidence for all possible compositions claimed. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that compounds fall within the scope of a claim will posses the alleged activity. See *In re Riat* et al. (CCPA 1964) 327 F2d 685, 140USPQ 471; In re Bart" et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

The breadth of the claims

Applicants are claiming a combination product containing a compound of claim 1 and an additional therapeutic agent. The argument that the agents claimed by the Applicants are

dependent upon the disease being treated is insufficient support that the Applicants are enabled for all additional inflammatory agents, insulin derivatives, etc.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art without direction, would be unable to test each and every combination encompassed by claims 24 and 27. One of skill in the art would need to determine whether the claimed composition would provide treatment of all the inflammatory conditions intended, and there are certainly hundreds of combinations of compositions encompassed by the claim. Based on the unpredictable nature of the invention and the state of the prior art and the breadth of the claims, one of ordinary skill in the art would be burdened with undue "experimentation study" to determine whether the claimed combination product would in fact treat the targeted disorder.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds and agents exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad recitation of any or all additional agents, etc of claims 24 or 27. As a result, necessitating one of skill to perform an exhaustive search for which claimed compositions can be utilized. The Examiner suggests claiming some specific agents that are enabled by the Specification or in literature, and to provide support for the recited combination products.

Claim Objections

9. Claims 1 and 2 are objected to for minor informalities, regarding the definition of "L", since a radical of formula (III) has been deleted from the claims, the second line of each claim should be amended to read, "wherein L is radical of the formula," for example.

Conclusion

10. In conclusion, claims 1-7, 9-11, 13, 21-27 are pending in the application, claims 22-25 and 27 are rejected and claims 1 and 2 are objected to. Claims 3-7, 9-11, 13, 21 and 26 appear to be allowable over the prior art.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Coppins whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699. The unofficial fax phone for this group are (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is viable through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/REI-TSANG SHIAO /

Janet L. Coppins
January 20, 2009

/REI-TSANG SHIAO/
Primary Examiner, Art Unit 1626